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# COMPOSITIONS FOR THE PREPARATION BY EXTRUSION OF MICROPARTICLES WHICH ALLOW THE SUSTAINED RELEASE OF A BIOLOGICALLY ACTIVE SUBSTANCE, AND MICROPARTICLES SO OBTAINED

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Abstract

Composition for the preparation by extrusion of microparticles allowing the sustained release of a biologically active substance constituted of an active substance, one or more polymers and 10-40% by weight of one or more lipid excipients, possessing the property of dissolving or gelling the polymers(s) and lubricating properties.

The present invention relates to novel compositions for the preparation by extrusion of microparticles that allow the sustained release of a biologically active substance, and the microparticles so obtained.

Different methods exist for the preparation of microgranules that allow the sustained release of an active substance. For example, there is a method that consists of performing the following successive steps: Attachment of a saccharose-starch seed crystal impregnation or enlargement of the seed crystal by the powdered or dissolved active substance, followed by coating with polymer solutions which impart the desired kinetics of release of the active substance. Another method comprises the performance of the following successive steps: extrusion of a humid mixture containing the active substance, sphere rendering of the extrudate, followed by coating of the microsphere obtained using polymer solutions which impart the kinetics of release of the active substance. However, these techniques are time consuming and expensive.

Moreover, it frequently happens that, particularly if extrusion is used, particles of small size are obtained that have a high surface exchange, which leads to a relatively rapid release of the active substance. To slow down the release rate, it is possible to apply a coating, after a prior sphere rendering, to obtain a film-producing membrane of a known thickness.

It has now been found, and this is the object of the present invention, that microparticles that allow the sustained release of a biologically active substance can be directly obtained by extrusion, without coating and/or sphere rendering, of a composition consisting of an active substance, of one or more polymer(s) and of one or more lipid excipient(s) and, optionally, one or more adjuvant(s) which are usually used in galenic pharmacy, such as antistatic agents, wetting agents or diluents.

The polymers that are used for the preparation of the microparticles according to the invention are selected from the cellulose ethers (such as the ethylcelluloses of the series G, K, N and T, and more particularly those of the series N, N. D. [Name of Distributor] Hercules), the polymers of acrylic and methacrylic acid esters (such as Eudragit RSPM, RLPM, L and 5 more particularly RSPM, N. D. Röhmpharma), the copolymers of vinylpyrrolidone and vinyl acetate (such as kollidon VA 64, N.D. B.A.S.F.), the polyvinyl alcohols such as the Mowiols (N.D.

Hocchst) and the vinyl acetate homopolymers such as, for example, Rhodopas BB 3 (N.D. Rhône-Poulenc).

The selection of the polymer is made as a function of the affinity of the active substance for the aqueous media. Thus, in general, in the case of a hydrophilic active substance, taking into account the small size of the microparticles and their large exchange surface, it is particularly advantageous to use a nonhydrophilic and nondegradable polymer (such as ethylcellulose of type N) to obtain a prolonged release over more than 8 h after oral administration to humans. In contrast, it is particularly advantageous to use degradable polymer, that is, a polymer which is slowly soluble in water and/or gradually digestible by the enzymes present in biological fluids (such as a vinylpyrrolidone/vinyl acetate copolymer, for example, Kollidon VA 64, N.D. BASF) to obtain a complete release of the active substance within 24 h.

The association of 2 or more polymers constitutes an additional means for controlling the kinetics of the release as a function of the specific characteristics of the active substance. It can also be advantageous, in some cases, to control the kinetics of the release by the addition of particularly hydrophobic polymers, such as polysiloxanes.

The lipid excipients are chosen from the fatty alcohols (cetyl alcohol), the fatty acids (stearic acid), the $C_{24}$-$C_{36}$ alcohol esters, and fatty acids having up to 36 carbon atoms (white wax), polyoxyethylenated plant oils (Cremophors, N.D. BASF; Labrafils, N.D. Gattefossé), the hydrogenated plant oils (Cutina H.R., N.D. Henkel), the fatty acid monodi- or triglycerides (Compritol 888 or Precirol, N.D. Gattefossé; Imwitar 900 or Softisan 154, N.D. Dynamit Nobel), or the lecithins.

The lipid excipient(s) must have a solubilizing or gelling capacity with regard to the polymer and a lubrication capacity to allow the extrusion.

It is particularly advantageous to prepare a composition containing a lipid excipient whose melting point is approximately 50°C to dissolve or gel the polymer associated with a second lipid excipient with a higher melting point to promote the lubrication.

It is possible to use a single lipid excipient, such as glycerol palmito-stearate (Precirol, N.D. Gattefossé), when it associates a low melting point with dissolving properties of gelling the polymer.

In the extrudable compositions according to the present invention, the content of lipid excipient generally represents 10-40 wt% of the composition and it is particularly advantageous to use a mixture of lipid excipients in which the lubricating excipient represents 60-80 wt% of the mixture.

In the extrudable compositions according to the present invention, the biologically active substance generally represents 5-40 wt% of the composition.

The release rate of the active substance is influenced by the size of the microparticles, the nature and quantity of the lipid excipient and the activity of the active substance with respect to the lipid excipient.

In general, the release rate of the active substance increases when the size of the microparticle decreases, this decrease in size being accompanied by an increase in the exchange surface.

The release rate is a function of the comparative affinity of the active substance with respect to, on the one hand, the lipid excipients constituting the microparticles and, on the other hand, the aqueous media in which the active substance is released, and it is also a function of the diffusion rate of the active substance in the matrix, which is connected with the nature and the quantity of the polymer(s). As a result, a lipophilic active substance, such as ketoprofen, will diffuse less rapidly in a lipid excipient for which the active substance has a greater affinity. Conversely, a less lipophilic active substance, such as riodipine or acebutolol hydrochloride, will diffuse more rapidly in a lipid excipient for which the active substance has less affinity.

For the preparation of the microparticles according to the invention, it is preferred to use a lipid excipient or a mixture of lipid excipients in which the polymer which plays the role of structuring agent is soluble or partially soluble.

According to the present invention, the microparticles are obtained by an extrusion method which consists in passing through calibrated perforations a homogeneous granulate constituting of a mixture of one or more polymers and of one or more lipid excipients containing the active substance.

The granulation can be carried out in a standard granulator using as wetting liquid the molten lipid excipient(s), or in an apparatus with a double heating jacket equipped with a rotatory knife and a doctor blade, with a gradual increase in the temperature until the lipid excipients start to melt in order to cause the granulation. By operating in this manner, it is possible to obtain a granulate whose homogeneity is much greater than when operating in a standard granulator.

Depending on the texture of the granulate obtained, it can be necessary to carry out, before the extrusion, a standardization operation for the purpose of breaking up agglomerates.

Advantageously, the extrusion can be carried out in an apparatus which consists essentially of two rollers rotating in opposite directions, one being solid, the other perforated. The granulate which is entrained at high pressure between the two rollers is extruded through the perforated roller in the form of small cylinders having essentially identical diameters, and a nearly constant length, thanks to a blade which shaves off the extrudate at the exit of the pores. The extrudates so obtained can be passed through a mesh to maintain a homogeneous composition.

The extrusion of the granulate is made possible thanks to the increase in the temperature which occurs between the two rollers. This increase in temperature leads to the partial melting of the lipid excipient whose melting point is the lowest, and which partially dissolves the polymer giving rise to a plastic composition which is extruded and which immediately resolidifies.

It is thus particularly important to control the extrusion temperature. This control can advantageously be carried out by acting on the feed rate of the granulate and/or on the rotation speed of the rollers in such a manner that the thermal energy is entirely absorbed by the granulate penetrating between the two rollers.

As a result, if the heat contribution is too low; for example, because of an excessively slow rotation speed of the rollers, the extrusion will only be partial and it will be necessary to recycle a large part of the granulate and, if the heat contribution is too high; for example, because of an excessively rapid rotation rate of the rollers, the caloric excess cannot be absorbed by the granulate before the extrusion, which leads to an increase in temperature resulting in more melting of the lipid excipient and, consequently, a clogging which makes the extrusion increasingly difficult.

It is particularly advantageous to carry out the extrusion through orifices having a diameter of approximately 1.5 mm.

The microparticles obtained by extrusion of the compositions according to the invention generally are in the form of cylindrical rods with a length of 1-5 mm and a diameter of 1-1.5 mm.

The microparticles according to the present invention can, for example, be uniformly distributed in capsules. Depending on the type of capsules used, the microparticles can, possibly, be subjected to a standardization treatment so that their shape and size are compatible with a regular filling.

It is also possible to fill the capsules with a mixture of microparticles having different dissolution kinetics.

The following examples, given on a nonlimiting basis, show how the invention can be implemented in practice.

Example 1

10 g of ketoprofen are added to 34 g of cetyl alcohol melted at a temperature of 65°C.

The solution so obtained is added, in small fractions, to 56 g of ethylcellulose N4 placed in a planetary mixer of the "Bouvard" type. The stirring speed is 50 rpm. The stirring is continued for 10 min until a homogeneous granulate is obtained.

The granulate so obtained is extruded in an Alexander Werk extruder whose perforations on the perforated roller have a diameter of 1 mm.

In this manner, microgranules are obtained which are in the form of rods with a diameter of 1-1.25 mm and a length of 1-5 mm.

Examples 2-8

The protocol is as in Example 1, except that the cetyl alcohol is replaced by different lipid excipients.

The results obtained are shown in Table 1

Table 1

| Exemples (1) | (2) Excipients lipidiques | (3) Caractéristiques |
|---|---|---|
| 2 | Acide stéarique (4) | (5) Petits bâtonnets dont le diamètre est compris entre 1 et 1,25 mm et dont la longueur est comprise entre 1 et 5 mm |
| 3 | Cire blanche (4) | |
| 4 | Imwitor 900 | |
| 5 | Cutina HR | |
| 6 | Précirol | |
| 7 | Compritol 8-88 | |
| 8 | Softisan 154 | |

Key: 1 Examples
2 Lipid excipients
3 Characteristics
4 Stearic acid
White wax
5 Small rods with a diameter of 1-1.25 mm and a length of 1-5 mm

Examples 9-17

The protocol is as in Example 1, except that the nature and the proportions of the lipid excipients and of the polymers are varied; the content of active substance (ketoprofen) being 10% of the total weight of the composition.

The results obtained are shown in Table 2

Table 2

| ① Exemples | ② Excipient lipidique % | ③ Polymère % | ④ Caractéristiques |
|---|---|---|---|
| | ⑤ – | | |
| 9 | Alcool cétylique 15 | Ethylcellulose N4 75 | |
| 10 | Alcool cétylique 10 | Ethylcellulose N4 80 | |
| 11 | Précirol 34 | Ethylcellulose N4 56 | ⑥ – |
| 12 | Précirol 15 | Ethylcellulose N4 75 | Petits bâtonnets dont le diamètre est compris entre 1 et 1,25 mm et dont la longueur est comprise 1 et 5 mm |
| 13 | Précirol 10 | Ethylcellulose N4 80 | |
| 14 | Précirol 34 | Moviol 4-88 56 | |
| 15 | Précirol 34 | Kollidon VA 64 56 | |
| 16 | Précirol 34 | Rhodopas BB 3 56 | |
| 17 | Précirol 34 | Eudragit RSPM 56 | |

Key: 1 Examples
2 Lipid excipient, %
3 Polymer, %
4 Characteristics
5 Cetyl alcohol
6 Small rods having a diameter of 1-1.25 mm and a length of 1-5 mm

The release of the active substance as a function of time is determined as follows:

The tests are carried out in a USP XX dissolutest. This apparatus consists of a water bath regulated at 37°C containing six reactors.

Each reactor is filled with 750 $cm^3$ of a medium whose pH is equal to 7.4, having the following composition:

| | | |
|---|---|---|
| - Disodium phosphate | | 1302 g |
| - Citric acid | | 40 g |
| - Distilled water | q.s.p. | 20 L |

A stirrer rotating at 120 rpm is immersed into each reactor.

A capsule containing 200 mg of microparticles is placed into each reactor at time t = 0.

A sample of 5 $cm^3$ is taken after 30 min, 1, 2, 3, 4, 5 and 23 h. In each sample, the quantity of released active substance is assayed. In the case of ketoprofen, the assay is carried out by spectrophotometry at 260 nm.

The results are collected in Table 3

Table 3

| ① Exemples | ③ ② % de substance active libérée après | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 mn | 1 H | 2 H | 3 H | 4 H | 5 H | 6 H | 23 H |
| 1 | 34 | 40 | 51 | | 61 | | 66 | 83 |
| 2 | 23 | 28 | 37 | 45 | 47 | 52 | | 76 |
| 3 | 12 | 22 | 38 | 47 | 50 | 54 | | 75 |
| 4 | 25 | 38 | | 60 | | | 76 | 92 |
| 5 | 2 | 3 | | 5 | | | 6 | 11 |
| 6 | 5 | 10 | | 30 | | | 45 | 68 |
| 7 | 3 | 4 | 6 | 11 | | 15 | | 44 |
| 8 | 3 | 5 | 6 | 8 | 9 | 10 | | 18 |
| 9 | 19 | 26 | 36 | | 48 | | 53 | 81 |
| 10 | 18 | 24 | 33 | | 43 | | 51 | 76 |
| 11 | 5 | 10 | | 30 | | | 45 | 68 |
| 12 | 4 | 8 | 17 | | 35 | | 47 | 81 |
| 13 | 4 | 8 | 15 | | 26 | | 33 | 60 |
| 14 | 36 | 70 | | 97 | | 98 | | 100 |
| 15 | 26 | 63 | | 90 | | 92 | | 96 |
| 16 | 14 | 36 | 58 | 71 | 75 | | 79 | 85 |
| 17 | 8 | 16 | | 32 | 36 | 40 | | 77 |

Key: 1 Examples
2 % of active substance released after
3 30 min

Example 18

Into the tank with double jacket of a granulator of the "OLZA" type, with a doctor blade and a rotatory knife at the bottom of the tank, 60 g of riodipine, 165 g of vinylpyrrolidone/vinyl acetate copolymer (Kollidon VA 64), 18.75 g of cetyl alcohol and 56.25 g of Précirol are introduced. The temperature of the stirred mixture is gradually raised by circulating hot water whose temperature is regulated at 65°C by means of a thermostat in the double jacket. A granulate forms, which is removed and then extruded in an "Alexanderwerk" extruder.

In this manner microparticles are obtained which are in the form of rods having a diameter of approximately 1.5 mm and a length of 1-5 mm.

Examples 19-30

The protocol is as in Example 18, except that extrudable mixtures whose composition is given in Table 4 are used.

Table 4

| N° exemple (1) | Principe actif (2) % | Polymère (3) % | Excipient lipidique (4) % |
|---|---|---|---|
| 19 | Kétoprofène (5) 20 | Kollidon VA 64 55 | (6) Alcool cétylique 6,25<br>(7) Precirol 18,75 |
| 20 | Riodipine 20 | Kollidon VA 64 65 | (6) Alcool cétylique 3,75<br>(7) Precirol 11,25 |
| 21 | Riodipine 20 | Kollidon VA 64 50 | (6) Alcool cétylique 7,5<br>(7) Precirol 22,5 |
| 22 | Riodipine 20 | Kollidon VA 64 55 | (6) Alcool cétylique 6,25<br>Cutina HR 18,75 |
| 23 | Riodipine 20 | Kollidon VA 64 55 | (6) Alcool cétylique 6,25<br>Compritol 8-88 18,75 |
| 24 | Kétoprofène (5) 20 | Mowiol 4-88 55 | (6) Alcool cétylique 6,25<br>(7) Precirol 18,75 |
| 25 | Kétoprofène 20 | Rhodopas BB 3 55 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |
| 26 | Kétoprofène 20 | Kollidon VA 64 54<br>Ethylcellulose N4 1 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |
| 27 | Kétoprofène 20 | Kollidon VA 64 45<br>Ethylcellulose N4 10 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |
| 28 | Kétoprofène 20 | Kollidon VA 64 25<br>Ethylcellulose N4 30 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |
| 29 | Kétoprofène 20 | Kollidon VA 64 45<br>Natrosol 250 HHX 10 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |
| 30 | Riodipine 20 (8) | Kollidon VA 64 45<br>Huile de silicone V 300 000 10 | Alcool cétylique (6) 6,25<br>Precirol (7) 18,75 |

Key: 1 Example No.
2 Active ingredient, %
3 Polymer, %
4 Lipid excipient, %
5 Ketoprofen
6 Cetyl alcohol
7 Précirol
8 Silicone oil

The release of the active substance as a function of time from the microparticles which are the object of Examples 18-30, is determined as follows:

The tests are carried out in a USP XX "dissolutest." This apparatus consists of a water bath regulated at 37°C containing six reactors.

Each reactor is filled with 1 L of dissolution medium constituting, in the case of riodipine, of a 2% Cremophor EL solution and, in the case of ketoprofen, of an aqueous solution having a pH of 5 and the following composition:

- Acetic acid: 205.9 g
- Dihydrated disodium phosphate: 363.12 g
- Demineralized water q.s.p.: 20 L

Into each reactor, a stirrer is immersed, the stirrer being either one blade rotating at 100 rpm or a basket rotating at 120 rpm.

A capsule containing 200 mg of microparticles is placed into the reactor at time t = 0.

A sample of 5 $cm^3$ is collected after 1, 2, 3, 4, 5, 6, and 22 h. The quantity of active substance released is assayed in each sample by spectrophotometry at 260 nm in the case of ketoprofen and 360 nm in the case of riodipine.

The results obtained are collected in Table 5

Table 5

| Microparticules des exemples (1) | % de substance activ libérée après (2) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 H | 2 H | 3 H | 4 H | 5 H | 6 H | 22 H |
| 18 | 18 | 30 | 36 | 42 | 48 | 51 | 88 |
| | 12± | 20 | 23 | 27 | 29 | 32 | 53 |
| 19 | 22 | 33 | 62 | 75 | 85 | 90 | 100 |
| 20 | 8± | 18 | 25 | 28 | 32 | 36 | 65 |
| 21 | 12± | 22 | 27 | 30 | 33 | 36 | 58 |
| 22 | 12± | 17 | 23 | 25 | - | 32 | 69 |
| 23 | 14± | 25 | 32 | 37 | - | 45 | 85 |
| 24 | 35 | 60 | 72 | 78 | 84 | 90 | 95 |
| 25 | 15 | 23 | 32 | 35 | 42 | 44 | 68 |
| 26 | 18 | 50 | 62 | 70 | 78 | 80 | 98 |
| 27 | 25 | 43 | 52 | 59 | 64 | 69 | 95 |
| 28 | 14 | 23 | 29 | 34 | 39 | 42 | 70 |
| 29 | 33 | 54 | 74 | 88 | 93 | 95 | 102 |
| 30 | 7,5 | 14,5 | 20,3 | 27,0 | 33,0 | 38,8 | 92,2 |

(3) ± Essais dans lesquels l'agitation est effectuée dans un panier tournant à 120 tours/minute.

Key: 1 Microparticles of the examples
2 % of active substance released after
3 Tests in which the stirring is carried out using a basket rotating at 120 rpm

Claims

1. Composition for the preparation by extrusion of microparticles allowing the sustained release of a biologically active substance characterized in that it constitutes a biologically active substance, one or more polymers which may or may not be erodible, and 10-40% of a mixture of at least two lipid excipients, of which one possesses the property of dissolving or gelling the polymer(s) and the other possesses lubricating properties, or of a lipid excipient which possesses simultaneously the property of dissolving or gelling the polymer(s) and lubricating properties, and optionally, one or more additives chosen from the diluents and the antistatic agents.

2. Composition according to Claim 1, characterized in that the polymer is chosen from the cellulose ethers, the polymers of acrylic and methacrylic acid esters, the vinylpyrrolidone/vinyl acetate copolymers, the polyvinyl alcohols and the vinyl acetate homopolymers and mixtures thereof.

3. Composition according to Claim 1, characterized in that the lipid excipient is chosen from the fatty alcohols, the fatty acids, the fatty alcohol and fatty acid esters, the hydrogenated plants or plant oils, the polyoxyethylenated plant oils, the mono-, di- or triglycerides of fatty acids, the lecithins and mixtures thereof.

4. Composition according to Claim 1, characterized in that the active substance represents 5-40 wt% of the composition.

5. Composition according to Claim 1, characterized in that, when a mixture of lipid excipients is used, the lubricating excipient represents 60-80 wt% of the mixture.

6. Composition according to Claim 1, characterized in that it contains, in addition, a very hydrophobic polymer.

7. Composition according to Claim 6, characterized in that the very hydrophobic polymer is chosen from the polysiloxanes.

8. Composition according to Claim 1, characterized in that the active substance is ketoprofen.

9. Microparticles allowing the sustained release of a biologically active substance characterized in that they are obtained by extrusion of a composition according to Claim 1.

European Patent Office

Application Number EP 86 40 0996

# EUROPEAN SEARCH REPORT

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int Cl⁴) |
|---|---|---|---|
| X,Y ① | EP-A-0 043 254 (GÖDECKE AKT).<br>* Page 1, lines 15-29, page 4, line 23-page 5, line 5: Clams 1,10* | 1-6,8,9 | A 61 K 9/22<br>A 61 K 9/16<br>A 61 K 9/52 |
| Y ② | US-A-3 965 256 (S.T. LESLIE)<br>*Column 8, lines 37-59, | 2-5, 8 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.⁴)

A 61 K

The present search report has been drawn up for all claims.

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| ③ THE HAGUE | ④ August 27, 1986 | BERTE M.J. |

## CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone.
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